

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 November 2002 (14.11.2002)

PCT

(10) International Publication Number
WO 02/089811 A1

(51) International Patent Classification⁷: **A61K 31/55**,
C07D 403/12, A61P 25/00

(21) International Application Number: PCT/EP02/04804

(22) International Filing Date: 2 May 2002 (02.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0111186.3 8 May 2001 (08.05.2001) GB

(71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; 980
Great West Road, Brentford, Middlesex TW8 9GS (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BROMIDGE, Steven, Mark** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **MOSS, Stephen, Frederick** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **VALENTINE, Jill**; Corporate Intellectual Property CN925.1, GlaxoSmithKline, 920 Great West Road, Brentford, Middlesex, TW8 9GS (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

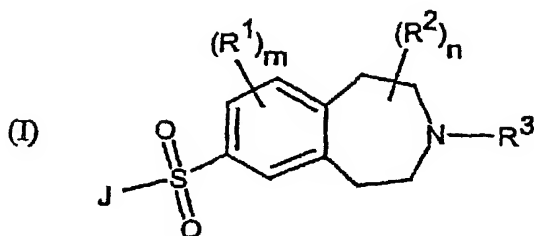
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BENZO[D]AZEPINE DERIVATIVES AS 5-HT₆ RECEPTOR ANTAGONISTS



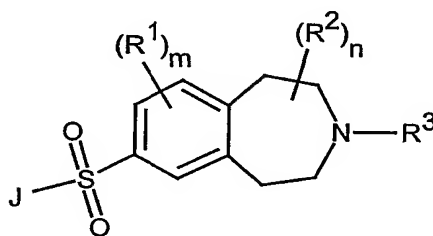
(57) Abstract: The invention relates to novel compounds (I) having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of disorders such like depression, anxiety and Alzheimers disease.

BENZO[D]AZEPINE DERIVATIVES AS 5-HT₆ RECEPTOR ANTAGONISTS

This invention relates to novel benzazepine compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081 discloses a series of aryl sulphonamide compounds that are said to be 5-HT₆ receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. WO 99/47516 and WO 99/65906 both disclose a series of indole derivatives that are claimed to possess 5-HT₆ receptor affinity.

A structurally novel class of compounds has now been found which also possess 5-HT₆ receptor affinity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

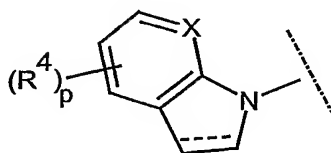
R¹ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, CN, CF₃ or OCF₃;

R² is C₁₋₆alkyl;

R³ is hydrogen or a C₁₋₁₀alkyl group optionally substituted by one, two or three substituents selected from the group consisting of halogen, C₁₋₆alkoxy, CN, amino, mono- or di-C₁₋₆alkylamino or a group -C(O)OR⁷ where R⁷ is hydrogen or C₁₋₆ alkyl; m is 0 - 3; n is 0 - 8;

J is selected from a group of formula (a), (b) or (c) in which

(a) is a group




(a)

wherein R⁴ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkylthio, hydroxy, CN, CF₃, NO₂, OCF₃, phenyl optionally substituted by groups as defined for R¹ above, benzyl, phenyloxy,

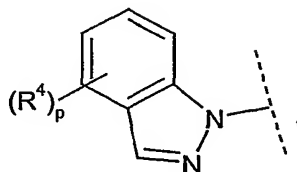
benzyloxy or C₃₋₆cycloalkyloxy or a group (CH₂)_q NR⁸R⁹ where q is 0, 1 or 2 and R⁸ and R⁹ are independently hydrogen or C₁₋₆alkyl;

p is 0, 1, 2, 3 or 4;

X is CH or N; and

5  is a single or double bond;

(b) is a group

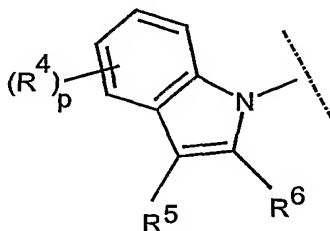


(b)

10

in which R⁴ and p are as defined for group (a) above; and

(c) is a group



(c)

15

in which R⁴ and p are as defined for group (a) above and R⁵ and R⁶ combine together to form a 5- to 7- membered carbocyclic or heterocyclic ring optionally substituted by groups as defined for R¹ above.

20

Alkyl groups, whether alone or as part of another group, may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

25

When present (i.e. when m is other than 0), the group(s) R¹ may be substituted at any suitable carbon atom within the benzene ring. When m is 2 or 3 the groups R¹ may be the same or different. Preferred R¹ groups are halogen (particularly fluorine, chlorine or bromine) or a C₁₋₆alkyl group (particularly methyl). Preferably m is 0 or 1, most preferably 0.

30

When present (i.e. when n is other than 0), the group(s) R² may be substituted at any suitable carbon atom within the azepine ring. When n is two or more the groups R² may be same or different. A particularly preferred R² group is methyl. Preferably, n is 0, 1 or 2. Preferably R³ is hydrogen, methyl or ethyl, most preferably hydrogen.

Within the definition of J formula (a)

The groups R^4 can be substituted at any suitable carbon atom within the indole ring (i.e. when ----- is a double bond) or indoline (i.e. when ----- is a single bond) ring. When p is other than 0, R^4 is preferably halogen (particularly fluorine, chlorine or bromine), a C_{1-6} alkyl group
 5 (particularly methyl), a C_{1-6} alkoxy group (particularly methoxy), benzyl, optionally substituted phenyl or a group $(CH_2)_qNR^8R^9$ (particularly CH_2NMe_2). When p is 2, 3 or 4 the groups R^4 may be the same or different. Preferably, ----- is a double bond.

10 Within the definition of J formula (b)

The groups R^4 can be substituted at any suitable carbon atom in the indazole ring. Preferred R^4 groups include those given for formula (a) above.

Within the definition of J formula (c)

15 The groups R^4 can be substituted at any suitable carbon atom. Preferred R^4 groups include those given for formula (a) above.

The 5- to 7- membered heterocyclic ring formed by the combination of groups R^5 and R^6 may be saturated, unsaturated or partially saturated. Preferably R^5 and R^6 combine together to form a 6 membered carbocyclic or heterocyclic ring. Most preferably, R^5 and R^6 combine such that the
 20 group J is a carbazole or tetrahydrocarbazole ring.

Particularly preferred compounds according to the invention include examples 1 - 33 (as shown below) or a pharmaceutically acceptable salt thereof.

25 The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic
 30 acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope
 35 stoichiometric hydrates as well as compounds containing variable amounts of water.

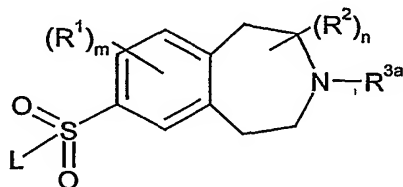
Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be
 40 separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

In a further aspect, the present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):

J - H

(II)

in which J is as defined in formula (I) with a compound of formula (III) or a protected derivative thereof;



(III)

in which R^1 , R^2 , m and n are as defined in formula (I), R^{3a} is an N protecting group or R^3 and L is a leaving group and optionally thereafter:

- converting a compound of formula (I) into another compound of formula (I);
- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

Suitable leaving groups include halogen, in particular chloro. The reaction of compounds of formulae (II) and (III) may be carried out by mixing the two reagents together, optionally under phase-transfer conditions, in a mixture of an inert organic solvent such as tetrahydrofuran with an aqueous base such as sodium hydroxide with the addition of a suitable phase-transfer catalyst such as tetrabutylammonium hydroxide. Alternatively, the reaction of compounds of formulae (II) and (III) may be carried out by treating a compound of formula (II) with a suitable base such as sodium hydride or sodium hexamethyldisilazane (NaHMDS) in an inert solvent such as tetrahydrofuran or N,N-dimethylformamide to form the anion of (II) and then treating this with a compound of formula (III) in an inert solvent. For compounds of formula (I) in which J is a group of formula (a) and ----- is a single bond, the reaction of compounds of formulae (II) and (III) is carried out by mixing the two reagents together, optionally in an inert solvent such as dichloromethane with or without the addition of a suitable base such as triethylamine or pyridine.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. The following example is given by way of illustration. For compounds of formula (I) wherein R^3 is hydrogen, it is possible to introduce an alternative R^3 group by conventional alkylation using 1 molar equivalent of an alkylhalide and 1 molar equivalent of a suitable base in an inert solvent.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection

techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals.

5 Deprotection of such groups is achieved using conventional procedures well known in the art.

Compounds of formulae (II) and (III) are commercially available, may be prepared using procedures described herein or by analogous methods thereto or according to known methods.

10 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have 5-HT₆ receptor activity and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders e.g. Alzheimers disease and age related cognitive decline, Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are further expected to be of use in the treatment of obesity and mild cognitive impairment.

25 Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline and ADHD. Also in particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity, mild cognitive impairment and schizophrenia.

35 The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

40 In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present

invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

5 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

10

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

15

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

20

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

25

30

35

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

40

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than

once a day, for example two or three times a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

10

Description 1

1-[7-(Indole-1-sulfonyl)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-ethanone (D1)

To a vigorously stirred solution of indole (31 mg, 0.26 mmol) in tetrahydrofuran (1mL) at room temperature, was added a 40% aqueous solution of tetrabutylammonium hydroxide (14 uL, 14.7
15 umol) followed by a 50% aqueous solution of sodium hydroxide (1 mL). After stirring the mixture for 10 minutes, a solution of 3-acetyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-sulfonyl chloride (for synthesis see patent: DE 2027436 (1970); Chem. Abstr. 1972, 76: 99535) (75 mg, 0.26 mmol) in tetrahydrofuran (1 mL) was added. A further quantity of the sulfonyl chloride (35 mg, 0.12 mmol) in tetrahydrofuran (1 mL) was added after 1 hour and vigorous stirring was
20 continued for a further 2 hours. To the reaction mixture was then added water (3 mL) and ethyl acetate (3 mL). After shaking the mixture, the layers were separated and the organic phase was washed with brine (3 mL), dried (MgSO₄) and filtered. The filtrate was concentrated *in vacuo* to an oil which was purified by column chromatography over silica gel, eluting with a gradient of dichloromethane/methanol, to afford the title compound (D1) (79 mg, 82%), δ H (CDCl₃)/ppm (rotamers) 2.21, 2.15 (3H, 2 x s), 2.89-2.94 (4H, m), 3.51-3.55 (2H, m), 3.65-3.68 (2H, m), 6.66 (1H, d, J = 4.0Hz), 7.19-7.32 (3H, m), 7.53-7.68 (4H, m), 7.98 (1H, d, J = 8.0Hz). MS: m/z (MH⁺) 369.

25

Description 2

30 1-[7-(2,3-Dihydro-indole-1-sulfonyl)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-ethanone (D2)

A solution of 2,3-dihydro-1H-indole (42mg, 0.35mmol) in dichloromethane (1ml) was added to a stirred solution of 3-acetyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-sulfonyl chloride (100mg, 0.35mmol) in dichloromethane (1ml) at room temperature under argon. *N,N*-diisopropylethylamine (61μl, 0.35mmol) was then added and the solution stirred for a further
35 18h. The reaction mixture was diluted with dichloromethane (10ml) and the solution was washed with brine (10ml), dried (MgSO₄) and concentrated in vacuo to an oil. The oil was purified by column chromatography over silica gel eluting with a gradient of dichloromethane/methanol to afford the title compound (D2) as an oil (114mg, 88%). MS: m/z (MH⁺) 371.

40

Description 3

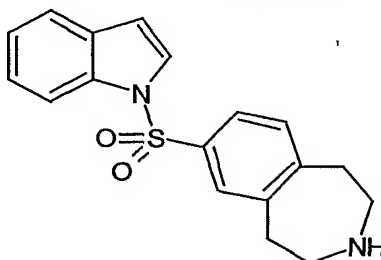
1-[7-(5-Bromo-2,3-dihydro-indole-1-sulfonyl)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-ethanone (D3)

The title compound (D3) was prepared as described in Description 2 by reacting 5-bromo-2,3-dihydro-1*H*-indole with 3-acetyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-7-sulfonyl chloride.

5 Yield = 73%. MS: m/z (MH^+) 449/451.

Example 1

7-(Indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d]azepine (E1)



10

A stirred solution of 1-[7-(indole-1-sulfonyl)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-ethanone (D1) (73 mg, 0.2 mmol) in *n*-butanol (1.5 mL) and 3M hydrochloric acid (3 mL) was heated at reflux for 7 hours. To the cooled mixture was added ethyl acetate (20 mL) and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) and the whole was shaken. After

15

separating the layers, the organic phase was washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* to an oil which was purified by column chromatography over silica gel, eluting with a gradient of dichloromethane/methanol, to afford the title compound (E1) (36 mg). Treatment of a solution of this material in

20

dichloromethane/diethyl ether (3 mL) with oxalic acid (1.5 equivalents) afforded the corresponding crystalline oxalate salt (39 mg, 47%), δH (CD_3OD)/ppm 3.29-3.38 (8H, m), 6.88 (1H, d, $J = 3.6Hz$), 7.38 (1H, t, $J = 7.6Hz$), 7.45 (1H, t, $J = 7.6Hz$), 7.51 (1H, d, $J = 8.0Hz$), 7.68 (1H, d, $J = 6.8Hz$), 7.80 (1H, d, $J = 3.6Hz$), 7.92-8.12 (2H, m), 8.12 (1H, d, $J = 7.6Hz$). MS: m/z (MH^+) 327.

25

The following compounds were prepared as oxalate salts by a sequential two step procedure as described in Description D1, treating the appropriate indole or indazole with 3-acetyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-7-sulfonyl chloride, and Example E1, in which *N*-deacetylation is carried out.

Compound	MH^+
7-(4-Chloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d]azepine (E2)	361/363
7-(6-Chloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d]azepine (E3)	361/363

7-(3-Methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E4)	341
7-[2-(4-Fluoro-phenyl)-indole-1-sulfonyl]-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E5)	421
7-(2-Methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E6)	341
Dimethyl-[1-(2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine-7-sulfonyl)-1 <i>H</i> -indol-3-ylmethyl]-amine (E7)	384
7-(3-Phenyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E8)	403
7-(3-Benzyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E9)	417
7-(7-Bromo-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E10)	405/407
7-(4-Methoxy-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E11)	357
7-(4-Methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E12)	341
7-(5-Bromo-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E13)	405/407
7-(5-Fluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E14)	345
7-(6-Methoxy-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E15)	357
7-(5-Chloro-2-methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E16)	375/377
7-(6-Fluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E17)	345
7-(7-Chloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E18)	361/363
9-(2,3,4,5-Tetrahydro-1 <i>H</i> -benzo[d]azepine-7-sulfonyl)-2,3,4,9-tetrahydro-1 <i>H</i> -carbazole (E19)	381
7-(4,5,6,7-Tetrafluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d]azepine (E20)	399
7-(2,3-Dimethyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E21)	355
7-(3-Chloro-indazole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E22)	362/364
7-(5,6-Dichloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1- <i>H</i> -benzo[d] azepine (E23)	395/397

7-(7-Nitro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E24)	372
9-(2,3,4,5-Tetrahydro-1H-benzo[d]azepine-7-sulfonyl)-9H-carbazole (E25)	377
7-(4,6-Difluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E26)	363
7-(6-Trifluoromethyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E27)	395
7-(5,6-Difluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E28)	363
Dimethyl-[1-(2,3,4,5-tetrahydro-1H-benzo[d]azepine-7-sulfonyl)-1H-indol-3-ylmethyl]-amine (E29)	384

Example 30**7-(Indole-1-sulfonyl)-3-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E30)**

Triethylamine (0.38ml, 2.8mmol) and sodium hydride (60% weight dispersion in mineral oil, 17mg, 0.4mmol) were added to a solution of 7-(indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E1) (100mg, 0.28mmol) in 1,2-dimethoxyethane (5ml) under argon at 0°C, and the reaction mixture was stirred for 30 mins. Iodomethane (26µl, 0.4mmol) was added and the reaction mixture allowed to warm to room temperature and stirred overnight. After addition of saturated NH₄Cl solution and basification with 5% NaOH, the whole was extracted with dichloromethane. The organic layer was washed with brine (5ml), dried (MgSO₄) and filtered. The filtrate was concentrated *in vacuo* to a solid which was purified by column chromatography over silica gel, eluting with a gradient of dichloromethane/methanol, to afford the title compound (E30) (37 mg, 39%) as a colourless oil. This was dissolved in dichloromethane (1ml) and stirred with 1M HCl in ether (11µl, 1equiv.) to afford the HCl salt of the title compound (E30) (32mg, 30%), δ H (CD₃OD)/ppm 2.34 (3H, s), 2.50-2.52 (4H, m), 2.88-2.93 (4H, m), 6.65 (1H, d, J=3.7Hz), 7.11-7.26 (3H, m), 7.51-7.61 (4H, m), 7.97 (1H, d). MS: m/z (MH⁺) 341.

Example 31**3-Ethyl-7-(indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E31)**

The hydrochloride salt of the title compound (E31) was prepared by the same procedure as described in Example 30, treating 7-(indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E1) with iodoethane. Yield = 54%. MS: m/z (MH⁺) 355.

Example 32**7-(2,3-Dihydro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E32)**

The oxalate salt of the title compound (E32) was prepared from 1-[7-(2,3-dihydro-indole-1-sulfonyl)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-ethanone (D2) as described in Example 1. Yield = 22%. MS: m/z (MH⁺) 329.

Example 33

7-(5-Bromo-2,3-dihydro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1H -benzo[d]azepine (E33)

The oxalate salt of the title compound (E33) was prepared from 1-[7-(5-bromo-2,3-dihydro-indole-1-sulfonyl)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-ethanone (D3) as described in Example 1. Yield = 23%. MS: m/z (MH⁺) 407/409.

5

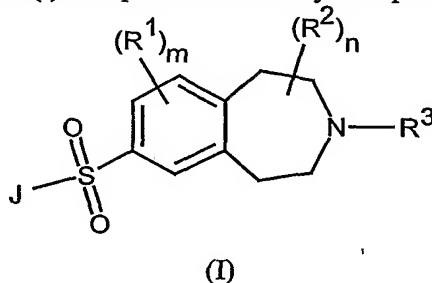
Pharmacological data

Compounds can be tested for 5-HT₆ receptor affinity according to the procedures outlined in WO 98/27081.

10 All examples were found to have a pK_i in the range 7.7 - 9.7 at human cloned 5-HT₆ receptors.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein

R^1 is halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, CN, CF_3 or OCF_3 ;

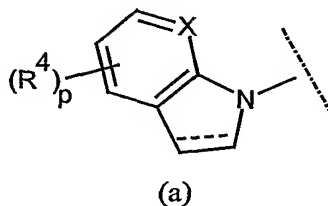
R^2 is C_{1-6} alkyl;

- 10 R^3 is hydrogen or a C_{1-10} alkyl group optionally substituted by one, two or three substituents selected from the group consisting of halogen, C_{1-6} alkoxy, CN, amino, mono- or di- C_{1-6} alkylamino or a group $-C(O)OR^7$ where R^7 is hydrogen or C_{1-6} alkyl; m is 0 - 3; n is 0 - 8;

J is selected from a group of formula (a), (b) or (c) in which

15

(a) is a group



wherein R^4 is halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkylthio, hydroxy, CN, CF_3 ,

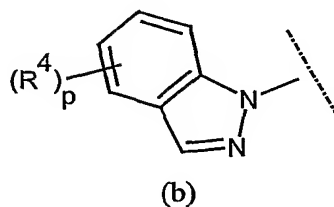
- 20 NO_2 , OCF_3 , phenyl optionally substituted by groups as defined for R^1 above, benzyl, phenyloxy, benzyloxy or C_{3-6} cycloalkyloxy or a group $(CH_2)_q NR^8R^9$ where q is 0, 1 or 2 and R^8 and R^9 are independently hydrogen or C_{1-6} alkyl;

p is 0, 1, 2, 3 or 4;

X is CH or N; and

- 25 ----- is a single or double bond;

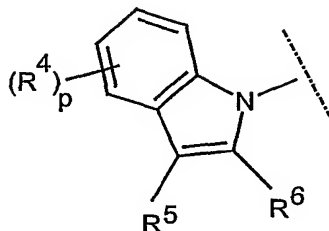
(b) is a group



30

in which R^4 and p are as defined for group (a) above; and

(c) is a group



(c)

in which R^4 and p are as defined for group (a) above and R^5 and R^6 combine together to form a 5- to 7- membered carbocyclic or heterocyclic ring optionally substituted by groups as defined for R^1 above.

2. A compound according to claim 1 in which J is a group of formula (a).
3. A compound according to claims 1 or 2 in which R^3 is hydrogen.
4. A compound according to any one of claims 1 to 3 wherein m is 0.
5. A compound according to any one of claims 1 to 4 wherein R^2 is methyl.
6. A compound according to any one of claims 1 to 5 wherein n is 0-2.
7. A compound according to any one of claims 1 to 6 wherein R^4 is halogen, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, benzyl, optionally substituted phenyl or a group $(CH_2)_qNR^8R^9$.
8. A compound according to claim 1 which is
 - 7-(Indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d]azepine;
 - 7-(4-Chloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-(6-Chloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-(3-Methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-[2-(4-Fluoro-phenyl)-indole-1-sulfonyl]-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-(2-Methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - Dimethyl-[1-(2,3,4,5-tetrahydro-1-*H*-benzo[d]azepine-7-sulfonyl)-1-*H*-indol-3-ylmethyl]-amine;
 - 7-(3-Phenyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-(3-Benzyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-(7-Bromo-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 - 7-(4-Methoxy-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;

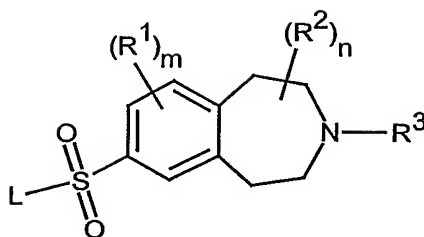
7-(4-Methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(5-Bromo-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(5-Fluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(6-Methoxy-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(5-Chloro-2-methyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d]
 azepine;
 7-(6-Fluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(7-Chloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 9-(2,3,4,5-Tetrahydro-1*H*-benzo[d]azepine-7-sulfonyl)-2,3,4,9-tetrahydro-1*H*-
 carbazole;
 7-(4,5,6,7-Tetrafluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-
 benzo[d]azepine;
 7-(2,3-Dimethyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(3-Chloro-indazole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(5,6-Dichloro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d] azepine;
 7-(7-Nitro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine;
 9-(2,3,4,5-Tetrahydro-1*H*-benzo[d]azepine-7-sulfonyl)-9*H*-carbazole;
 7-(4,6-Difluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine;
 7-(6-Trifluoromethyl-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1*H*-
 benzo[d]azepine;
 7-(5,6-Difluoro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine;
 Dimethyl-[1-(2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-7-sulfonyl)-1*H*-indol-3-
 ylmethyl]-amine;
 7-(Indole-1-sulfonyl)-3-methyl-2,3,4,5-tetrahydro-1-*H*-benzo[d]azepine;
 3-Ethyl-7-(indole-1-sulfonyl)-2,3,4,5-tetrahydro-1-*H*-benzo[d]azepine;
 7-(2,3-Dihydro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine;
 7-(5-Bromo-2,3-dihydro-indole-1-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[d]
 azepine;
 or a pharmaceutically acceptable salt thereof.

9. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II):

J - H

(II)

5 in which J is as defined in formula (I) with a compound of formula (III) or a protected derivative thereof;



(III)

in which R^1 , R^2 , m and n are as defined in formula (I), R^{3a} is an N protecting group or R^3 and L is a leaving group and optionally thereafter:

- 5
 - converting a compound of formula (I) into another compound of formula (I);
 - removing any protecting groups;
 - forming a pharmaceutically acceptable salt.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier or excipient.

11. A compound according to any one of claims 1 to 8 for use in therapy.

12. A compound according to any one of claims 1 to 8 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

13. The use of a compound of formula (I) as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

14. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 8 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

15. A method of treating depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia which comprises administering a safe and therapeutically effective amount to a patient in need thereof of a compound of formula (I) as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int ☐ onal Application No

PCT/EP 02/04804

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/55 C07D403/12 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 27081 A (BROMIDGE STEVEN MARK ;KING FRANCIS DAVID (GB); SMITHKLINE BEECHAM) 25 June 1998 (1998-06-25) cited in the application the whole document ---	1-15
A	WO 00 00203 A (LILLY CO ELI ;XU YAO CHANG (US); HAUSER KENNETH LEE (US); HERTEL L) 6 January 2000 (2000-01-06) the whole document --- -/--	1-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 September 2002

Date of mailing of the international search report

13/09/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fritz, M

INTERNATIONAL SEARCH REPORT

Int  onal Application No

PCT/EP 02/04804

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MARYANOFF B E ET AL: "Azepinoindole derivatives with high affinity for brain dopamine and serotonin receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 8, 21 April 1998 (1998-04-21), pages 983-988, XP004137004 ISSN: 0960-894X the whole document</p> <p>-----</p>	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/04804

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9827081	A	25-06-1998	AU 729056 B2	25-01-2001
			AU 6090498 A	15-07-1998
			BG 103530 A	31-01-2000
			BR 9713734 A	28-03-2000
			CN 1246116 A	01-03-2000
			CZ 9902203 A3	17-11-1999
			WO 9827081 A1	25-06-1998
			EP 0946539 A1	06-10-1999
			HU 0000658 A2	28-02-2001
			JP 2001506646 T	22-05-2001
			NO 993003 A	18-06-1999
			NZ 335970 A	26-10-2001
			PL 334337 A1	28-02-2000
			SK 80899 A3	14-02-2000
			TR 9901361 T2	23-08-1999
			TW 418205 B	11-01-2001
			US 6423717 B1	23-07-2002
			ZA 9711319 A	17-06-1999
WO 0000203	A	06-01-2000	AU 4727799 A	17-01-2000
			EP 1091741 A1	18-04-2001
			JP 2002519326 T	02-07-2002
			WO 0000203 A1	06-01-2000